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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12Q 1/70	A3	(11) International Publication Number: WO 99/67428 (43) International Publication Date: 29 December 1999 (29.12.99)
(21) International Application Number: PCT/EP99/04317 (22) International Filing Date: 22 June 1999 (22.06.99) (30) Priority Data: 98870143.9 24 June 1998 (24.06.98) EP (71) Applicant (for all designated States except US): INNOGENET-ICS N.V. [BE/BE]; Industriepark Zwijnaarde 7, P.O. Box 4, B-9052 Ghent (BE). (72) Inventor; and (75) Inventor/Applicant (for US only): STUYVER, Lieven [BE/BE]; Holestraat 8, B-9552 Herzele (BE). (74) Common Representative: INNOGENETICS N.V.; Industriepark Zwijnaarde 7, P.O. Box 4, B-9052 Ghent (BE).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 13 April 2000 (13.04.00)
(54) Title: METHOD FOR DETECTION OF DRUG-SELECTED MUTATIONS IN THE HIV PROTEASE GENE		
(57) Abstract <p>The present invention relates to a method for the rapid and reliable detection of drug-selected mutations in the HIV protease gene allowing the simultaneous characterization of a range of codons involved in drug resistance using specific sets of probes optimized to function together in a reverse-hybridization assay. More particularly, the present invention relates to a method for determining the susceptibility to antiviral drugs of HIV viruses in a biological sample, with said method comprising: a) if need be, releasing, isolating or concentrating the polynucleic acids present in the sample; b) if need be amplifying the relevant part of the protease gene of HIV with at least one suitable primer pair; c) hybridizing the polynucleic acids of step a) or b) with at least one of the following probes: probes specifically hybridizing to a target sequence comprising codon 30; probes specifically hybridizing to a target sequence comprising codon 46 and/or 48; probes specifically hybridizing to a target sequence comprising codon 50; probes specifically hybridizing to a target sequence comprising codon 54; probes specifically hybridizing to a target sequence comprising codon 82 and/or 84; probes specifically hybridizing to a target sequence comprising codon 90; <u>or the complement of said probes</u>; further characterized in that said probes specifically hybridize to any of the target sequences presented in figure (1), <u>or the complement of said target sequences</u>; d) inferring from the result of step c) whether or not a mutation giving rise to drug resistance is present in any of said target sequences.</p>		

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DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

In national Application No

PCT/EP 99/04317

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12Q1/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EASTMAN ET AL: "Genotypic changes in human immunodeficiency virus type 1 associated with loss of suppression of plasma viral RNA levels in subjects treated with ritonavir (norvir) monotherapy" JOURNAL OF VIROLOGY, June 1998 (1998-06), XP002129272 the whole document --- -/--	1-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

31 January 2000

Date of mailing of the international search report

11/02/2000

Name and mailing address of the ISA

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NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Reuter, U

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/04317

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LIPSHUTZ R J ET AL: "USING OLIGONUCLEOTIDE PROBE ARRAYS TO ACCESS GENETIC DIVERSITY" BIOTECHNIQUES,US,EATON PUBLISHING, NATICK, vol. 19, no. 3, 1 September 1995 (1995-09-01), pages 442-447, XP000541924 ISSN: 0736-6205 the whole document ---	1,2,9
X	WO 97 41259 A (LACROIX JEAN MICHEL ;HUI MAY (CA); DUNN JAMES M (CA); LEUSHNER JAM) 6 November 1997 (1997-11-06) example 15 ---	11
Y	CORDOBA J. ET AL: "'Human immunodeficiency virus and resistance!. VIRUS DE LA INMUNODEFICIENCIA HUMANA Y RESISTENCIAS." REVISTA ESPANOLA DE QUIMIOTERAPIA, (1998) 11/2 (152-156). , XP000867234 the whole document ---	1-9
Y	SCHINAZI ET AL: "Mutations in retroviral genes associated with drug resistance" INTERNATIONAL ANTIVIRAL NEWS, vol. 5, no. 8, August 1997 (1997-08), pages 129-142, XP000861634 cited in the application the whole document ---	1-9
A	WO 97 27332 A (INNOGENETICS NV ;STUYVER LIEVEN (BE); LOUWAGIE JOOST (BE); ROSSAU) 31 July 1997 (1997-07-31) the whole document ---	1-12
A	WINTERS ET AL : "Human immunodeficiency virus type 1 protease genotypes and in vitro protease inhibitor susceptibilities of isolates from individuals who where switched to other protease inhibitors after long-term sequinavir treatment" JOURNAL OF VIROLOGY, vol. 22, no. 6, June 1998 (1998-06), pages 5303-5306, XP002129273 the whole document ---	1-12
	-/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/04317

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>SCHOOLMEESTER, A. (1) ET AL: "A line probe assay (LiPA) for the detection of drug-selected mutations in the HIV -1 protease gene."</p> <p>ABSTRACTS OF THE INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1998) VOL. 38, PP. 396-397. MEETING INFO.: 38TH INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY SAN DIEGO, CALIFORNIA, USA SEPTEMBER 24-27, 1998 AMER, XP000869787</p> <p>abstract</p> <p>-----</p>	1-12

INTERNATIONAL SEARCH REPORT

...international application No.

PCT/EP 99/04317

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 9, 10 and 12
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 9,10,12

Present claim 9 relates to a vast amount of nucleic acids so that a lack of conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Consequently the claimed nucleic acid sequences have not been searched per se.

Present claim 10 relates to an extremely large number of possible nucleic acid sequences so that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Consequently, the search has been carried out for those parts of the claim which do appear to be clear and concise, namely the nucleic acid sequences themselves, which are specified with a sequence ID number. Neither nucleic acids comprising these sequences nor fragments of these sequences, wherein said fragment consists of at least two contiguous nucleotides and contains at least one polymorphic nucleotide, have been searched.

Present claim 12 relates to a vast amount of nucleic acids that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Consequently the nucleic acid sequences being part of the claimed kit have not been searched per se.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/04317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9741259 A	06-11-1997	US 5789168 A	04-08-1998
		US 5888736 A	30-03-1999
		US 5830657 A	03-11-1998
		AU 2378097 A	19-11-1997
		AU 2747597 A	19-11-1997
		AU 2816797 A	19-11-1997
		AU 2816897 A	19-11-1997
		CA 2252487 A	06-11-1997
		CA 2252571 A	06-11-1997
		CA 2252588 A	06-11-1997
		WO 9740939 A	06-11-1997
		EP 0896632 A	17-02-1999
		EP 0907752 A	14-04-1999
		EP 0914468 A	12-05-1999
		WO 9741257 A	06-11-1997
		WO 9741258 A	06-11-1998
		US 5897842 A	27-04-1999
WO 9727332 A	31-07-1997	AU 1444397 A	20-08-1997
		BR 9704637 A	09-06-1998
		CA 2215073 A	31-07-1997
		EP 0817866 A	14-01-1998
		JP 11502727 T	09-03-1999



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(54) Title: METHOD FOR DETECTION OF DRUG-SELECTED MUTATIONS IN THE HIV PROTEASE GENE (57) Abstract <p>The present invention relates to a method for the rapid and reliable detection of drug-selected mutations in the HIV protease gene allowing the simultaneous characterization of a range of codons involved in drug resistance using specific sets of probes optimized to function together in a reverse-hybridization assay. More particularly, the present invention relates to a method for determining the susceptibility to antiviral drugs of HIV viruses in a biological sample, with said method comprising: a) if need be, releasing, isolating or concentrating the polynucleic acids present in the sample; b) if need be amplifying the relevant part of the protease gene of HIV with at least one suitable primer pair; c) hybridizing the polynucleic acids of step a) or b) with at least one of the following probes: probes specifically hybridizing to a target sequence comprising codon 30; probes specifically hybridizing to a target sequence comprising codon 46 and/or 48; probes specifically hybridizing to a target sequence comprising codon 50; probes specifically hybridizing to a target sequence comprising codon 54; probes specifically hybridizing to a target sequence comprising codon 82 and/or 84; probes specifically hybridizing to a target sequence comprising codon 90; <u>or the complement of said probes</u>; further characterized in that said probes specifically hybridize to any of the target sequences presented in figure (1), <u>or the complement of said target sequences</u>; d) inferring from the result of step c) whether or not a mutation giving rise to drug resistance is present in any of said target sequences.</p>		

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20-04-2000

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Intellectual Property Department
Industriepark Zwijnaarde 7
Box 4
B-9052 Ghent
BELGIUM

COMMUNICATION IN CASES FOR WHICH
NO OTHER FORM IS APPLICABLE

Applicant's or agent's file reference PCT99.92PROT	Date of mailing (day/month/year) 18/04/2000
International application No. PCT/EP 99/04317	REPLY DUE See paragraph 1 below
Applicant INNOGENETICS N.V. ET AL.	International filing date (day/month/year) 22/06/1999

1. ☐ REPLY DUE within _____ ~~1000~~ days from the above date of mailing
- ☒ NO REPLY DUE


2. COMMUNICATION:

The International Bureau of WIPO has drawn the attention of this International Searching Authority to the fact that the form PCT/ISA/217 (Notification of decision concerning request for rectification) mailed to you on 11.01.2000 was sent too late for publication.

As the international publication of this application took place and the time limit under Rule 91 is expired, the substitute sheets cannot be incorporated in the record copy. Due to a clerical error this limit date (24.11.99) was not taken into account before sending the PCT/ISA/217 to you.

We advise you that any rectification can now be effected directly with the designated offices during the national phase.

We apologize for any inconvenience caused.

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Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Barbara Klaver *BK*

Handwritten notes:
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YUN
29/04

32
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From the INTERNATIONAL SEARCHING AUTHORITY

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INNOGENETICS N.V.
Industriepark Zwijnaarde 7
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NOTIFICATION OF DECISION CONCERNING
REQUEST FOR RECTIFICATION

(PCT Rule 91.1(f))

Applicant's or agent's file reference

PCT99.92PROT

International application N°.

PCT/EP 99/ 04317

Applicant

INNOGENETICS N.V. ET AL.

Date of mailing

(day/month/year)

11/01/2000

REPLY DUE

NONE

However, see last paragraph below

International filing date

(day/month/year)

22/06/1999

The applicant is hereby notified that this International Searching Authority has considered the request for rectification of obvious errors in the international application/in other papers submitted by the applicant to this Authority, and that it has decided:

1. ☒ to authorize the rectification:

☒ as requested by the applicant.

☐ to the extent set forth below*:

2. ☐ to refuse to authorize the rectification or part of it for the following reasons*:

A copy of this notification, together with a copy of the applicant's request for rectification, has been sent to the receiving Office and to the International Bureau.

* If the authorization of the rectification has been refused in whole or in part, the applicant may request the International Bureau, before the technical preparations for international publication have been completed and subject to the payment of a fee, to publish the request for rectification together with the international application. See Rule 91.1(f), third and fourth sentences, and, for the amount of the fee, see the PCT Applicant's Guide, Volume I/A, Annex B2(1B).

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Fax: (+31-70) 340-3016

Authorized officer

Barbara Klaver

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Table 3 - Cont'd-1

	44	45	46	47	48	49	50	51	52	53	54	length	Seq	ID
	CCA	AAA	ATG	ATA	GGG	GGA	ATT	GGA	GGT	TTT	ATC			
P48w1				GTA	GGG	GGA	ATT	GGA	GGT	GG		18		47
P48w2				GTA	GGG	GGA	ATT	GGA	GGT	TG		19		48
P48w3				GTA	GGG	GGA	ATT	GGA	GGT	TTG		20		49
P48w4				GTA	GGG	GGA	ATT	GGA	GGT	TTT		21		50
P48w5			G	GTA	GGG	GGA	ATT	GGA	GGT	TTG		21		51
P48w6			ATG	GTA	GGG	GGA	ATT	GGA				18		52
P48w7			ATG	GTA	GGG	GGA	ATT	GGA	G			19		53
P48w8		A	ATG	GTA	GGG	GGA	ATT	GGA				19		54
P48w9		A	ATG	GTA	GGG	GGA	ATT	GGA	G			20		55
P48w10		A	ATG	GTA	GGG	GGA	ATT	GGA	GGG	GG		22		56
P48w21			ATA	ATA	GGG	GGA	ATT	GGA				18		57
P48w22			ATG	ATA	GGG	GGA	ATT	GGA				18		58
P48w23		A	ATA	ATA	GGG	GGA	ATT	GGA				19		59
P48w24		A	ATG	ATA	GGG	GGA	ATT	GGA				19		60
P48w25				ATA	GGG	GGA	ATT	GGA	GGT	GG		18		61
P48w26				ATA	GGG	GGA	ATT	GGA	GGT	TG		19		62
P48w28				ATA	GGG	GGA	ATT	GGA	GGT	TTG		20		63
P48w29				ATA	GGG	GGA	ATT	GGA	GGT	TTT		21		64
P48m11				GTA	GTG	GGA	ATT	GGA	GGT	GG		18		65
P48m12				GTA	GTG	GGA	ATT	GGA	GGT	TG		19		66
P48m13				GTA	GTG	GGA	ATT	GGA	GGT	TTG		20		67
P48m14				GTA	GTG	GGA	ATT	GGA	GGT	TTT		21		68
P48m15			G	GTA	GTG	GGA	ATT	GGA	GGT	TTG		21		69
P48m16			ATG	GTA	GTG	GGA	ATT	GGA				18		70
P48m17			ATG	GTA	GTG	GGA	ATT	GGA	G			19		71
P48m18		A	ATG	GTA	GTG	GGA	ATT	GGA				19		72
P48m19		A	ATG	GTA	GTG	GGA	ATT	GGA	G			20		73
P48m20		A	ATG	GTA	GTG	GGA	ATT	GGA	GGG	GG		22		74
P48m29				ATA	GTG	GGA	ATT	GGA	GGT	GG		18		75
P48m30				ATA	GTG	GGA	ATT	GGA	GGT	TG		19		76
P48m31			ATG	ATA	GTG	GGA	ATT	GGA				18		77
P48m32			ATG	ATA	GTG	GGA	ATT	GGA	G			19		78
P48m33		A	ATG	ATA	GTG	GGA	ATT	GGA				19		79
p48w34			G	ATA	GGG	GGA	ATT	G				14		80
p48w35			TG	ATA	GGG	GGA	ATT	G				15		81
p48w36			TG	ATA	GGG	GGA	ATT	GG				16		82
p48w37			ATG	ATA	GGG	GGA	ATT					15		83
p48m38			G	ATA	GTG	GGA	ATT	G				14		84
p48m39			TG	ATA	GTG	GGA	ATT	G				15		85
p48m40			TG	ATA	GTG	GGA	ATT	GG				16		86
p48m41			ATG	ATA	GTG	GGA	ATT					15		87
p48w42			ATA	ATA	GGG	GGA	ATT					15		88
p48w43			TG	ATA	GGG	GGA	GTT					14		89
p48w44			G	ATA	GGG	GGA	GTT	G				14		90
p48w45		A	ATG	ATA	GGA	GGA	ATT					16		91
p48w46			ATG	ATA	GGG	GGA	ATT					15		92
p48w47		AAA	ATG	ATA	GGG	GGA						15		93
p48w48		A	AAA	ATG	ATA	GGG	GG					15		94

step b) comprises amplifying a fragment of the protease gene with at least one 3'-primer specifically hybridizing to a target sequence located between nucleotide position 253 (codon 85) and nucleotide positions 300, more preferably between nucleotide position 253 (codon 85) and nucleotide positions 290, more preferably between nucleotide position 253 (codon 85) and nucleotide positions 280, even more preferably at nucleotide position 253 (codon 85) to nucleotide position 273 (codon 91), in combination with at least one suitable 5'-primer, and step c) comprises hybridizing the polynucleic acids of step a) or b) with at least one of the probes specifically hybridizing to a target sequence comprising any of codons 30, 46, 48, 50, 52, 54, 82 and 84.

It has been found, unexpectedly, that an amplified nucleic acid fragment comprising all of the above-mentioned codons, does not hybridize optimally to probes comprising codon 82, 84 or 90. On the other hand, a shorter fragment, for instance the fragment which is amplified by use of the primers Prot41bio and Prot6bio with respectively seq id no 5 and seq id no 4, hybridizes better to probes comprising codon 90. Better hybridization is also obtained when the fragment is amplified with primer Prot41bio in combination with primers Prot6abio, Prot6bbio, Prot6cbio and Prot6dbio. The present invention thus also relates to a method as defined above, further characterized in that the 5'-primer is seq id no 5 and at least one 3' primer is chosen from seq id no 4, seq id no 506, seq id no 507, seq id no 508, and seq id no 509. Likewise, another shorter fragment, for instance the fragment which is amplified by use of the primers Prot2bio and Prot31bio with respectively seq id no 3 and seq id no 6, was found to hybridize better to probes comprising codon 82 and/or 84. Hence the present invention also relates to a method as defined above, further characterized in that the 5'-primer is seq id no 5 and at least one 3'-primer is chosen from seq id no 4, seq id no 506, seq id no 507, seq id no 508, and seq id no 509..

New sets of amplification primers as mentioned in example 1 were selected. The present invention thus also relates to primers: prot 16 (SEQ ID NO 501), prot 5 (SEQ ID NO 502), prot2a bio (SEQ ID NO 503), prot2b bio (SEQ ID NO 504), prot31 bio (SEQ ID NO 6), prot41-bio (SEQ ID NO 505), prot6a (SEQ ID NO 506), prot6b (SEQ ID NO 507), prot6c (SEQ ID NO 508) and prot6d (SEQ ID NO 509). A number of these primers are chemically modified (biotinylated), others are not. The present invention relates to any of the primers mentioned, primers containing unmodified nucleotides, or primers containing modified nucleotides.

Different techniques can be applied to perform the sequence-specific hybridization methods of the present invention. These techniques may comprise immobilizing the amplified HIV polynucleic acids on a solid support and performing hybridization with labeled oligonucleotide probes. HIV polynucleic acids may also be immobilized on a solid support without prior amplification and subjected to hybridization. Alternatively, the probes may be immobilized on a solid support and hybridization may be performed with labeled HIV polynucleic acids, preferably after amplification. This technique is called reverse hybridization. A convenient reverse hybridization technique is the line probe assay (LiPA). This

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PCT
HV#

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
INNOGENETICS N.V.
Industriepark Zwijnaarde 7
Box 4
B-9052 Ghent
BELGIUM

NOTIFICATION OF DECISION CONCERNING
REQUEST FOR RECTIFICATION

(PCT Rule 91.1(f))

	Date of mailing (day/month/year) 11/01/2000
Applicant's or agent's file reference PCT99.92PROT	REPLY DUE NONE However, see last paragraph below
International application N°. PCT/EP 99/ 04317	International filing date (day/month/year) 22/06/1999
Applicant INNOGENETICS N.V. ET AL.	



The applicant is hereby notified that this International Searching Authority has considered the request for rectification of obvious errors in the international application/in other papers submitted by the applicant to this Authority, and that it has decided:

- ☒ to authorize the rectification:

☒ as requested by the applicant.
☐ to the extent set forth below*:
- ☐ to refuse to authorize the rectification or part of it for the following reasons*:

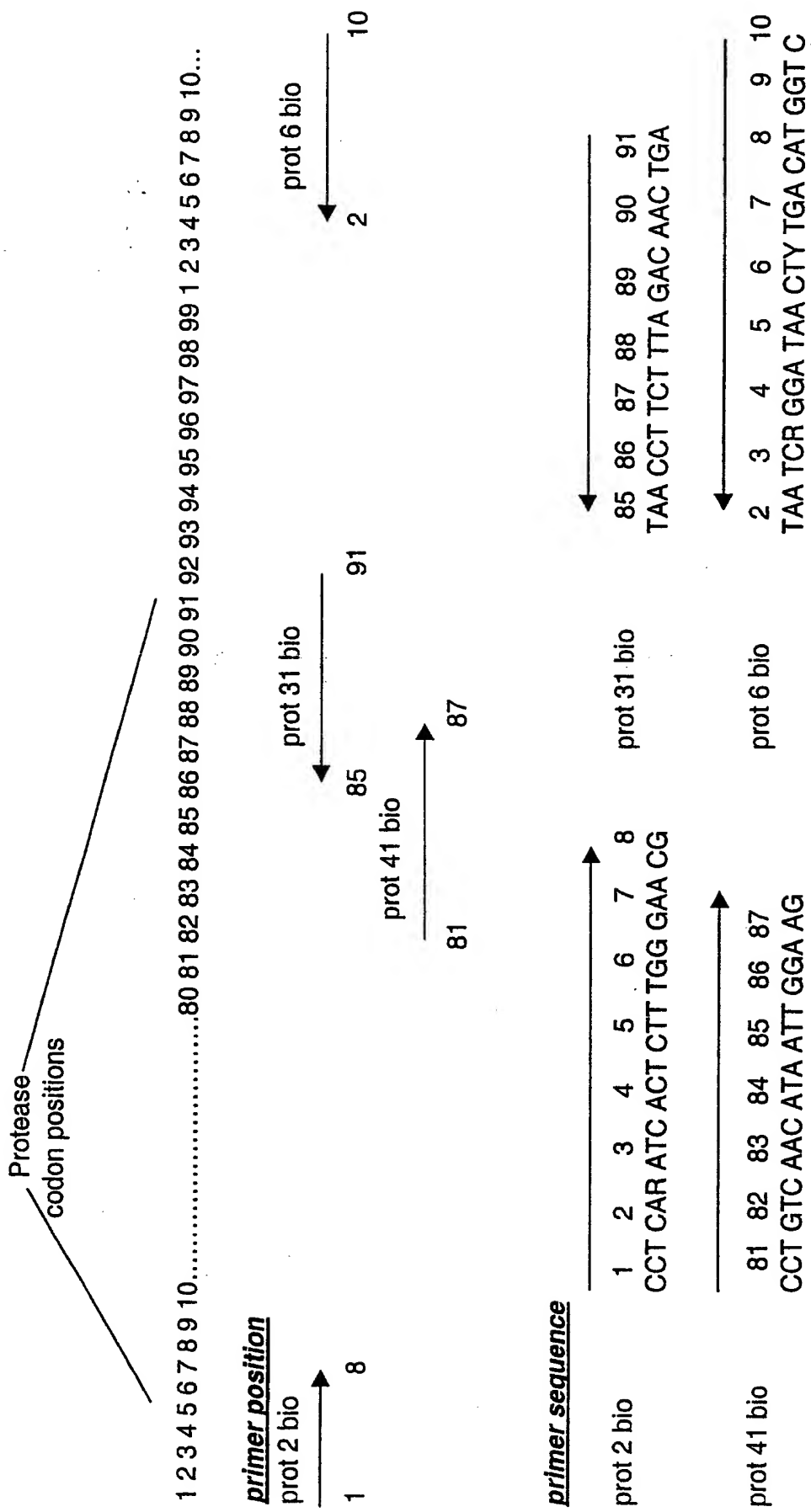
A copy of this notification, together with a copy of the applicant's request for rectification, has been sent to the receiving Office and to the International Bureau.

* If the authorization of the rectification has been refused in whole or in part, the applicant may request the International Bureau, before the technical preparations for international publication have been completed and subject to the payment of a fee, to publish the request for rectification together with the international application. See Rule 91.1(f), third and fourth sentences, and, for the amount of the fee, see the PCT Applicant's Guide, Volume I/A, Annex B2(1B).

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Barbara Klaver 
--	--

9/21

Figure 3



PATENT COOPERATION TREATY

PCT

REC'D 18 AUG 2000

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

16

Applicant's or agent's file reference PCT99.92PROT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/04317	International filing date (day/month/year) 22/06/1999	Priority date (day/month/year) 24/06/1998
International Patent Classification (IPC) or national classification and IPC C12Q1/70		
Applicant INNOGENETICS N.V. ET AL.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 14/01/2000	Date of completion of this report 16.08.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Weaver, M Telephone No. +49 89 2399 8689 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/04317

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

Description, pages:

1-50 as originally filed

Claims, No.:

1-12 as originally filed

Drawings, sheets:

1/21-21/21 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/04317

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8, 12
	No:	Claims	9-11
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section V

1. Despite the lack of clarity of the claims (see Section VIII), it is possible to determine that claim 1 is intended to cover a method for the determination of susceptibility to antiviral drugs of HIV viruses by means of hybridisation assays to discover mutations in any of codons 30, 46, 48, 50, 54, 82, 84 and 90, presumably as given in Figure 1, although this is not stated in the claim.
2. D1 (J Virol 72 (1998) 5154; abstract; page 5157, column 1, line 3 - last line; page 5161, column 1, line 54, column 2, line 8; Table 1) discloses that mutations in the HIV-1 protease amino acid sequence, and in the corresponding encoding sequences, are associated with resistance to protease inhibitors. In particular, mutations in codons 46, 54, 63, 71, 77, 82 and 84 have been identified.

As at least some of the probes disclosed in Table 1 of D1 will hybridise to a target sequence comprising codons 46, 54, 82, 84 and 90 (**comprising** meaning, in this context, a target sequence **including** the said codon), it would be obvious for the skilled person to use known probes to test for HIV susceptibility to antiviral drugs when it is already known that the sequences to which these probes hybridise contain codon having mutations known to be associated with antiviral drug resistance.

3. Moreover, D2 (Internat Antiviral News 5 (1997) 129) discloses a list of all known HIV-1 drug resistance mutations, including those of D1 and the remaining codons referred to in claim 1 of the present application.

Again, there can be nothing inventive in the selection of particular mutations to search for, when these mutations are known to be associated with HIV-1 drug resistance.

4. Claim 1 thus lacks an inventive step and does not meet the requirements of Article 33(3) PCT.
5. Dependent claims 2 - 8 do not appear to contain any features which, in combination with the features of any claim to which they refer, meet the require-

ments of the PCT in respect of inventive step, given the disclosures of D1 and D2 (Article 33(3) PCT).

6. Probes falling within the scope of claim 9 are known from D1, Table 1 for the reasons given in point 2 above. It should be noted in this context that the language "for use in a method" is to be interpreted as meaning "suitable for use" in that method and confers no other limitation on the scope of the claim (see the PCT Guidelines Ch. III-4.8, last sentence).

Claim 9 thus lacks novelty and does not meet the requirements of Article 33(2) PCT.

7. Claim 10 encompasses dinucleotides which contain at least one polymorphic nucleotide. If we take the example of SEQ ID NO:479 or 480, and consider the mutations in codon 54, one polymorphic site is the third base, which is C in the consensus sequence and T in SEQ ID NO:479 and 480 (see page 5, lines 32 - 36 and Figure 1). Thus, according to the language used, claim 10 encompasses i.a. the dinucleotides TT and TA, both of which are prima facie known. Moreover, claim 10 also encompasses many more such dinucleotides which are also prima facie known as such.

Claim 10 thus lacks novelty and does not meet the requirements of Article 33(2) PCT.

8. If limited to nucleotides consisting of SEQ ID NO. 478 - 500, the subject-matter of claim 10 could be acknowledged as novel and inventive (Article 33(2) and (3) PCT)

None of the available prior art documents discloses any of these sequences and there is no teaching that the particular combinations of mutations found in each sequence are associated with anti-viral drug resistance.

9. The primer having SEQ ID NO:504 is known from D3 (WO-A-97/41259; Example 15, primer PR211F). As the language "for use in a method" is to be interpreted as meaning "suitable for use" in that method and confers no other limitation on the

scope of the claim (see the PCT Guidelines Ch. III-4.8, last sentence), and the primer of D3 is clearly suitable for the use stated in claim 11, the latter lacks novelty (Article 33(2) PCT).

The remaining primers of claim 11 do not appear to be inventive over the primer of D3, given the disclosures of D1 and D2 for the reasons given in points 2 and 3 above (Article 33(3) PCT).

10. The sole obligatory and non-optional features of the kit of claim 12 are components (c) (but excluding the feature "possibly fixed to a solid support"), (d) and (e) (see the PCT Guidelines Ch. III-4.6).

As it would be obvious for the skilled person to assemble, in the form of a kit, the components essential for performing a non-inventive method using non-inventive probes (i.e. the methods of claims 1- 3 and the probes referred to therein; see points 2, 3 and 6 above), claim 12 is also considered to lack an inventive step over the disclosures of D1 and D2 (Article 33(3) PCT).

Section VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 - D3 is not mentioned in the description, nor are these documents identified therein.

Section VIII

1. The claims lack clarity (Article 6 PCT) for the following reasons:

Claim 1:

The terms "codon 30", "codon 46 and/or 48" etc. are undefined in context; it would appear that a reference to the sequences of Figure 1 is required in the claim. Moreover, it would have to be clarified which particular sequence is intended, i.e. the consensus sequence of Figure 1, one of the "polymorphic sequences" or all of these. In addition, it is unclear from Figure 1 whether the alternative bases given beneath the consensus sequence are intended to all be present in a given

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/04317

sequence, if presented on a single line, or whether each of these can be present individually. Similar objections apply to the language "any of the target sequences presented in figure 1".

Claims 3, 4, 7 and 8:

The terminology used does not meet the WIPO standard for presentation of nucleotide sequences (see the Administrative Instructions under the PCT, Annex C), i.e. the sequence identification number should be presented as SEQ ID NO:X.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 February 2000 (22.02.00)	
International application No. PCT/EP99/04317	Applicant's or agent's file reference PCT99.92PROT
International filing date (day/month/year) 22 June 1999 (22.06.99)	Priority date (day/month/year) 24 June 1998 (24.06.98)
Applicant STUYVER, Lieven	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
14 January 2000 (14.01.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer A. Karkachi Telephone No.: (41-22) 338.83.38
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PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PCT99.92PROT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 99/ 04317	International filing date (day/month/year) 22/06/1999	(Earliest) Priority Date (day/month/year) 24/06/1998
Applicant INNOGENETICS N.V. ET AL.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1: Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

METHOD FOR DETECTION OF DRUG-SELECTED MUTATIONS IN THE HIV PROTEASE GENE

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 04317

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 9, 10 and 12
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 9,10,12

Present claim 9 relates to a vast amount of nucleic acids so that a lack of conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Consequently the claimed nucleic acid sequences have not been searched per se.

Present claim 10 relates to an extremely large number of possible nucleic acid sequences so that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Consequently, the search has been carried out for those parts of the claim which do appear to be clear and concise, namely the nucleic acid sequences themselves, which are specified with a sequence ID number. Neither nucleic acids comprising these sequences nor fragments of these sequences, wherein said fragment consists of at least two contiguous nucleotides and contains at least one polymorphic nucleotide, have been searched.

Present claim 12 relates to a vast amount of nucleic acids that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Consequently the nucleic acid sequences being part of the claimed kit have not been searched per se.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/04317

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q1/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EASTMAN ET AL: "Genotypic changes in human immunodeficiency virus type 1 associated with loss of suppression of plasma viral RNA levels in subjects treated with ritonavir (norvir) monotherapy" JOURNAL OF VIROLOGY, June 1998 (1998-06), XP002129272 the whole document --- -/--	1-9

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

31 January 2000

Date of mailing of the international search report

11/02/2000

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Reuter, U

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/04317

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LIPSHUTZ R J ET AL: "USING OLIGONUCLEOTIDE PROBE ARRAYS TO ACCESS GENETIC DIVERSITY" BIOTECHNIQUES, US, EATON PUBLISHING, NATICK, vol. 19, no. 3, 1 September 1995 (1995-09-01), pages 442-447, XP000541924 ISSN: 0736-6205 the whole document	1, 2, 9
X	WO 97 41259 A (LACROIX JEAN MICHEL ; HUI MAY (CA); DUNN JAMES M (CA); LEUSHNER JAM) 6 November 1997 (1997-11-06) example 15	11
Y	CORDOBA J. ET AL: "'Human immunodeficiency virus and resistance!. VIRUS DE LA INMUNODEFICIENCIA HUMANA Y RESISTENCIAS." REVISTA ESPANOLA DE QUIMIOTERAPIA, (1998) 11/2 (152-156). , XP000867234 the whole document	1-9
Y	SCHINAZI ET AL: "Mutations in retroviral genes associated with drug resistance" INTERNATIONAL ANTIVIRAL NEWS, vol. 5, no. 8, August 1997 (1997-08), pages 129-142, XP000861634 cited in the application the whole document	1-9
A	WO 97 27332 A (INNOGENETICS NV ; STUYVER LIEVEN (BE); LOUWAGIE JOOST (BE); ROSSAU) 31 July 1997 (1997-07-31) the whole document	1-12
A	WINTERS ET AL : "Human immunodeficiency virus type 1 protease genotypes and in vitro protease inhibitor susceptibilities of isolates from individuals who where switched to other protease inhibitors after long-term zidovudine treatment" JOURNAL OF VIROLOGY, vol. 22, no. 6, June 1998 (1998-06), pages 5303-5306, XP002129273 the whole document	1-12

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/04317

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>SCHOOLMEESTER, A. (1) ET AL: "A line probe assay (LiPA) for the detection of drug-selected mutations in the HIV -1 protease gene."</p> <p>ABSTRACTS OF THE INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1998) VOL. 38, PP. 396-397. MEETING INFO.: 38TH INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY SAN DIEGO, CALIFORNIA, USA SEPTEMBER 24-27, 1998 AMER, XP000869787 abstract</p> <p>-----</p>	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/04317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9741259 A	06-11-1997	US 5789168 A	04-08-1998
		US 5888736 A	30-03-1999
		US 5830657 A	03-11-1998
		AU 2378097 A	19-11-1997
		AU 2747597 A	19-11-1997
		AU 2816797 A	19-11-1997
		AU 2816897 A	19-11-1997
		CA 2252487 A	06-11-1997
		CA 2252571 A	06-11-1997
		CA 2252588 A	06-11-1997
		WO 9740939 A	06-11-1997
		EP 0896632 A	17-02-1999
		EP 0907752 A	14-04-1999
		EP 0914468 A	12-05-1999
		WO 9741257 A	06-11-1997
		WO 9741258 A	06-11-1998
		US 5897842 A	27-04-1999
WO 9727332 A	31-07-1997	AU 1444397 A	20-08-1997
		BR 9704637 A	09-06-1998
		CA 2215073 A	31-07-1997
		EP 0817866 A	14-01-1998
		JP 11502727 T	09-03-1999